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**Drug monographs on drugs which are frequently analysed in the context of
Therapeutic Drug Monitoring / Arzneimittel-Monographien für
Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings
analysiert werden**

Rentsch, Katharina ; Baumann, Pierre ; Fathi, Marc ; Grignaschi, Nathalie ; Magnin, Jean-Luc ;
Thormann, Wolfgang ; Todesco, Liliane ; Wenk, Markus ; Werner, Dominique

Abstract: In addition to the monographs which were published last year by the working group "Drug Monitoring" of the Swiss Society of Clinical Chemistry (SSCC) [1], new monographs have been written. The aim of these monographs is to give an overview of the most important information necessary for ordering a drug analysis or interpreting the results. Therefore, the targeted readers comprise laboratory health professionals and all receivers of laboratory reports. There is information provided on the indication for therapeutic drug monitoring, protein binding, metabolic pathways and enzymes involved, elimination half-life and elimination routes, and on therapeutic or toxic concentrations. Preanalytical considerations are of particular importance for therapeutic drug monitoring. Therefore, information is provided regarding a reasonable timing for the determination of drug concentrations as well as steady-state concentrations after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest in drug analysis, references to important publications are given. The number of monographs will be continuously enlarged. The updated files are presented on the homepage of the SSCC (www.sccc.ch). We hope that these monographs are helpful and look forward to receiving comments from the audience

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Drug monographs on drugs which are frequently analysed in the context of Therapeutic Drug Monitoring

Arzneimittel-Monographien für Medikamente, die regelmäßig im Rahmen des Therapeutic Drug Monitorings analysiert werden

Working group “Drug Monitoring” of the SSCC (Arbeitsgruppe Medikamente der SGKC):

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Abstract

In addition to the monographs which were published last year by the working group “Drug Monitoring” of the Swiss Society of Clinical Chemistry (SSCC) [1], new monographs have been written. The aim of these monographs is to give an overview of the most important information necessary for ordering a drug analysis or interpreting the results. Therefore, the targeted readers comprise laboratory health professionals and all receivers of laboratory reports. There is information provided on the indication for therapeutic drug monitoring, protein binding, metabolic pathways and enzymes involved, elimination half-life and elimination routes, and on therapeutic or toxic concentrations.

Preanalytical considerations are of particular importance for therapeutic drug monitoring. Therefore, information is provided regarding a reasonable timing for the determination of drug concentrations as well as steady-state concentrations after changing the dose. Furthermore, the stability of the drug and its metabolite(s) after blood sampling is described. For readers with a specific interest in drug analysis, references to important publications are given.

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The number of monographs will be continuously enlarged. The updated files are presented on the homepage of the SSCC (www.sccc.ch).

We hope that these monographs are helpful and look forward to receiving comments from the audience.

Keywords: cyclosporine A; haloperidol; lamotrigine; mirtazepine; mycophenolate; paroxetine; phenobarbital; sertraline; valproic acid.

Zusammenfassung

In Ergänzung zu den im letzten Jahr publizierten Arzneimittelmonographien der Arbeitsgruppe Medikamente der Schweizerischen Gesellschaft für Klinische Chemie (SGKC) [1] sind nun weitere Monographien erstellt worden. Ziel dieser Monographien ist es, dem Labormediziner bzw. dem Empfänger der Befunde eine Übersicht über die wichtigsten Informationen zu geben, die für die Veranlassung einer Analyse bzw. für die Interpretation der Resultate hilfreich sind.

Es werden klinisch-pharmakologische Angaben wie zum Beispiel Indikation für das Therapeutic Drug Monitoring, Proteinbindungen, Metabolisierungswege und daran beteiligte Enzyme, Halbwertszeiten und Eliminationswege der Muttersubstanz sowie Informationen zu therapeutischen bzw. toxischen Bereichen zur Verfügung gestellt.

Da die Präanalytik gerade beim Therapeutic Drug Monitoring eine wichtige Rolle spielt, werden auch hier Angaben gemacht, zu welchem Zeitpunkt eine Bestimmung der Arzneimittelkonzentration sinnvoll ist und wann, nach einer Dosisänderung, der “steady-state” erreicht ist. Außerdem werden Informationen zur Stabilität der Medikamente bzw. ihrer Metaboliten nach der Blutentnahme gegeben. Für die interessierten Leser sind die verwendeten Referenzen als Zitate aufgeführt.

Die Zahl der Monographien wird fortlaufend ergänzt. Die aktuellsten Versionen der Monographien sind auf der Homepage der SGKC abrufbar (www.sccc.ch).

Wir hoffen, dass Ihnen diese Monographien im Umgang mit dem Therapeutic Drug Monitoring hilfreich sein werden und freuen uns über Kommentare und Bemerkungen.

Schlüsselwörter: Ciclosporin A; Haloperidol; Lamotrigin; Mirtazepin; Mycophenolat; Paroxetin; Phenobarbital; Sertralin; Valproinsäure.

Cyclosporine

General

• Class of the drug	Immunosuppressants
• Synonym(s)	
• Common trade name(s) in Germany	Cicloral [®] HEXAL [®] , Immunosporin [®] , Sandimmun [®] , Sandimmun Optoral [®]
• Conversion factors	$\mu\text{g/L} \times 0.83 = \text{nmol/L}$ $\text{nmol/L} \times 1.20 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	41–58% localized in erythrocytes; in plasma 90% bound to proteins, mainly lipoproteins
• Elimination half-life	5–18 h
• Volume of distribution	3–5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4
– Active metabolite(s)	AM1 and AM9 have about 10% of the activity of cyclosporine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	P-glycoprotein substrate and inducer (e.g. St. John's Wort)
• Elimination of parent drug	Hepatic > 94%, renal < 6%
• Typical therapeutic range	Dependent on combination therapy and indication
• Potentially toxic concentration	> 500 $\mu\text{g/L}$ (C ₀)

Pre-analytics

• Time to steady-state from beginning of treatment or change of posology	~2 days
• Time for blood sampling	Before next dose at steady state (C ₀) or 2 h after administration (C ₂)
• Type(s) of sample	Whole blood on EDTA
• Stability	5 days at 25°C

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Armstrong VW, Oellerich M. New developments in the immunosuppressive drug monitoring of cyclosporine, tacrolimus, and azathioprine. Clin Biochem 2001;34:9–16.
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- Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (p-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.

Haloperidol

General

- | | |
|-----------------------------------|--|
| • Class of the drug | Neuroleptics |
| • Synonym(s) | |
| • Common trade name(s) in Germany | Haldol®, Haldol® decanoas |
| • Conversion factors | $\mu\text{g/L} \times 2.66 = \text{nmol/L}$
$\text{nmol/L} \times 0.38 = \mu\text{g/L}$ |

Clinical pharmacology

- | | |
|---|---|
| • Indications for TDM | Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity |
| • Protein binding | 92% |
| • Elimination half-life | 24 h (12–38 h) |
| • Volume of distribution | 7.9 ± 2.5 L/kg |
| • Metabolism | |
| – Main metabolic pathways | CYP3A4, CYP2D6 and reduction |
| – Active metabolite(s) | None |
| – Inhibitor or inducer of the cytochrome P450 system? | Reduced haloperidol (metabolite; inhibits CYP2D6) |
| – Other significant pharmacokinetic interactions | None |
| • Elimination of parent drug | Mainly hepatic |
| • Typical therapeutic range | 3.8–38.0 $\mu\text{g/L}$ (10–100 nmol/L) |
| • Potentially toxic concentration | 49.4 $\mu\text{g/L}$ (> 130 nmol/L) |

Pre-analytics

- | | |
|--|----------------------------------|
| • Time to steady-state from beginning of treatment or change of posology | ~5 days |
| • Time for blood sampling | Before next dose at steady state |
| • Type(s) of sample | Serum or plasma |
| • Stability | 1 week at 4°C |

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 2004;37:243–65.
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- Pan L, Rosseel MT, Belpaire FM. Comparison of two high-performance liquid chromatographic methods for monitoring plasma concentrations of haloperidol and reduced haloperidol. *Ther Drug Monit* 1998;20:224–30.

Lamotrigine

General

- Class of the drug
- Synonym(s)
- Common trade name(s) in Germany
- Conversion factors

Antiepileptics

Lamictal®, elmendos®
 $\text{mg/L} \times 3.90 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.256 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM
- Protein binding
- Elimination half-life
- Volume of distribution
- Metabolism
 - Main metabolic pathways
 - Active metabolite(s)
 - Inhibitor or inducer of the cytochrome P450 system?
 - Other significant pharmacokinetic interactions

Individual dose adaptation, verification of compliance
 55%
 25 h (60 h in presence of valproate, 15 h in presence of phenytoin, carbamazepine or phenobarbital)
 1–1.4 L/kg

N-glucuronidation
 None
 Not known

- Coadministration with valproic acid results in decreased elimination of lamotrigine
- Coadministration with enzyme inducing drugs, including carbamazepine, phenytoin and phenobarbital, results in increased elimination

- Elimination of parent drug
- Typical therapeutic range
- Potentially toxic concentration

Mainly hepatic, renal 10%
 3–14 mg/L (12–56 $\mu\text{mol/L}$)
 Not known

Pre-analytics

- Time to steady-state from beginning of treatment or change of posology
- Time for blood sampling
- Type(s) of sample
- Stability

4–5 days

Before next dose at steady state
 Serum or plasma
 1 week at 4°C

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Johannessen SI, Battino D, Berry DJ, Bialer M, Kramer G, Tomson T, et al. Therapeutic drug monitoring of the newer antiepileptic drugs. *Ther Drug Monit* 2003;25:347–63.
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Mirtazapine

General

• Class of the drug	Antidepressants
• Synonym(s)	
• Common trade name(s) in Germany	Remergil®
• Conversion factors	
Mirtazapine:	$\mu\text{g/L} \times 3.77 = \text{nmol/L}$ $\text{nmol/L} \times 0.26 = \mu\text{g/L}$
Desmethyilmirtazapine:	$\mu\text{g/L} \times 3.97 = \text{nmol/L}$ $\text{nmol/L} \times 0.25 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	85%
• Elimination half-life	20–40 h
• Volume of distribution	4.5 L/kg
• Metabolism	
– Main metabolic pathways	CYP3A4, CYP2D6, CYP1A2
– Active metabolite(s)	Desmethyilmirtazapine
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Hepatic > 80%, renal < 20%
• Typical therapeutic range	
Mirtazapine:	10.4–31.2 $\mu\text{g/L}$ (40–120 nmol/L)
Desmethyilmirtazapine:	5.0–20.0 $\mu\text{g/L}$ (20–80 nmol/L)
• Potentially toxic concentration	Not known

Pre-analytics

• Time to steady-state of treatment or change of posology	~5 days from beginning
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 2004;37:243–65.
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- Shams M, Hiemke C, Hartter S. Therapeutic drug monitoring of the antidepressant mirtazapine and its N-demethylated metabolite in human serum. *Ther Drug Monit* 2004;26:78–84.

Mycophenolate (MPA)

General

• Class of the drug	Immunosuppressants
• Synonym(s)	Mycophenolic acid
• Common trade name(s) in Germany	CellCept®, Myfortic®
• Conversion factors	$\text{mg/L} \times 3.12 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.32 = \text{mg/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, symptoms of rejection or toxicity
• Protein binding	97–99% (mainly to albumin)
• Elimination half-life	17 h
• Volume of distribution	4 L/kg
• Metabolism:	
– Main metabolic pathways	Glucuroconjugation to form 7-O-MPA-glucuronide (MPAG); two other metabolites are 7-O-glucoside-MPA and acylglucuronide-MPA (AcMPAG)
– Active metabolite(s)	AcMPAG
– Inhibitor or inducer of the cytochrome P450 system?	No
– Other significant pharmacokinetic interactions	None
• Elimination of parent drug	Mainly hepatic
• Typical therapeutic range	Dependent on combination therapy and indication
• Potentially toxic concentration	> 10 mg/L

Pre-analytics

• Time to steady-state from beginning of treatment or change of posology	~3 days
• Time for blood sampling	Before next dose at steady state or at different time points for the determination of the area-under-the-curve (AUC)
• Type(s) of sample	Plasma on EDTA
• Stability	5 days at 25°C

Remarks

- Mycophenolate mofetil (MMF) is a prodrug for the active MPA.
- Most immunoassays cross-react with the active metabolite.
- The AUC correlates better with the inhibition of the inosine monophosphate dehydrogenase (IMPDH) than the trough level.

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Holt DW, Armstrong VW, Griesmacher A, Morris RG, Raymond G, Napoli K, et al. International Federation of Clinical Chemistry/International Association of Therapeutic Drug Monitoring and Clinical Toxicology working group on immunosuppressive drug monitoring. Therap Drug Monit 2002;24:59–67.
- Shaw LM, Nicholls A, Hale M, Holt DW, Venkataramanan R, Haley J, et al. Therapeutic drug monitoring of mycophenolic acid: A consensus panel. Clin Biochem 1998;31:317–22.

Paroxetine

General

• Class of the drug	Antidepressants
• Synonym(s)	
• Common trade name(s) in Germany	Seroxat®, Tagonis®
• Conversion factors	$\mu\text{g/L} \times 3.03 = \text{nmol/L}$ $\text{nmol/L} \times 0.33 = \mu\text{g/L}$

Clinical pharmacology

• Indications for TDM	Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity
• Protein binding	95%
• Elimination half-life	24 h (6–71 h)
• Volume of distribution	17 L/kg
• Metabolism	
– Main metabolic pathways	CYP2D6 and other CYP enzymes
– Active metabolite(s)	None
– Inhibitor or inducer of the cytochrome P450 system?	Inhibitor of CYP2D6
– Other significant pharmacokinetic interactions	Not known
• Elimination of parent drug	Hepatic 36%, renal 64%
• Typical therapeutic range	39.6–122 $\mu\text{g/L}$ (120–370 nmol/L)
• Potentially toxic concentration	Not known

Pre-analytics

• Time to steady-state from beginning of treatment or change of posology	~5 days
• Time for blood sampling	Before next dose at steady state
• Type(s) of sample	Serum or plasma
• Stability	1 week at 4°C

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 2004;37:243–65.
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- Montgomery SA. Efficacy of long-term treatment of depression. *J Clin Psychiatry* 1996;57:24–30.

Phenobarbital

General

- Class of the drug
- Synonym(s)
- Common trade name(s) in Germany
- Conversion factors

Antiepileptics

Luminal®, Luminaletten®

 $\text{mg/L} \times 4.31 = \mu\text{mol/L}$ $\mu\text{mol/L} \times 0.232 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM
- Protein binding
- Elimination half-life
- Volume of distribution
- Metabolism
 - Main metabolic pathways
 - Active metabolite(s)
 - Inhibitor or inducer of the cytochrome P450 system?
 - Other significant pharmacokinetic interactions
- Elimination of parent drug
- Typical therapeutic range
- Potentially toxic concentration

Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity

50% (to albumin)

50–150 h (varies with age, urinary pH, hepatic and renal function)

0.7 L/kg

Hydroxylation by P450 cytochromes to form p-hydroxyphenobarbital followed by glucuro- or sulfoconjugation

None

Inducer of cytochromes CYP3A4 and CYP2C9 (also auto-induction)

Interaction with valproic acid (phenobarbital levels increase)

Hepatic 75%, renal 25%

15–40 mg/L (64–172 $\mu\text{mol/L}$)> 50 mg/L (> 216 $\mu\text{mol/L}$)

Pre-analytics

- Time to steady-state from beginning of treatment or change of posology
- Time for blood sampling
- Type(s) of sample
- Stability

10–30 days

Before next dose at steady state

Serum or plasma

48 h at 4°C (for longer conservation, freeze at -20°C)

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage), Basel: Documed, 2005.
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Sertraline

General

- Class of the drug
- Synonym(s)
- Common trade name(s) in Germany
- Conversion factors

Antidepressants

Gladem®, Zoloft®

$\mu\text{g/L} \times 3.26 = \text{nmol/L}$

$\text{nmol/L} \times 0.31 = \mu\text{g/L}$

Clinical pharmacology

- Indications for TDM
- Protein binding
- Elimination half-life
- Volume of distribution
- Metabolism
 - Main metabolic pathways
 - Active metabolite(s)
 - Inhibitor or inducer of the cytochrome P450 system?
 - Other significant pharmacokinetic interactions
- Elimination of parent drug
- Typical therapeutic range
- Potentially toxic concentration

Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity

98%

22–36 h for sertraline

62–104 h for N-desmethylsertraline

> 20 L/kg

CYP3A4, CYP2D6, CYP2B6, CYP2C9

N-Desmethylsertraline

Weak inhibitor of CYP2D6 and CYP3A4

None

Hepatic 50%, renal 50%

12.4–62.0 $\mu\text{g/L}$ (40–200 nmol/L)

Not known

Pre-analytics

- Time to steady-state from beginning of treatment or change of posology
- Time for blood sampling
- Type(s) of sample
- Stability

~ 5 days

Before next dose at steady state

Serum or plasma

1 week at 4°C

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Baumann P, Hiemke C, Ulrich S, Eckermann G, Gaertner I, Gerlach M, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry* 2004;37:243–65.
- Linder MW, Keck PE Jr. Standards of laboratory practice: antidepressant drug monitoring. *National Academy of Clinical Biochemistry. Clin Chem* 1998;44:1073–84.
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- Montgomery SA. Efficacy of long-term treatment of depression. *J Clin Psychiatry* 1996;57:24–30.

Valproic acid

General

- Class of the drug
- Synonym(s)
- Common trade name(s) in Germany
- Conversion factors

Antiepileptics
Valproate
Convulex®, Ergenyl®, Orfiril®
 $\text{mg/L} \times 6.93 = \mu\text{mol/L}$
 $\mu\text{mol/L} \times 0.144 = \text{mg/L}$

Clinical pharmacology

- Indications for TDM

Individual dose adaptation, verification of compliance, side effects, suspicion of toxicity

- Protein binding

85 to 95% at low concentration, decreases to 70% with higher dosing (mainly to albumin)

- Elimination half-life

5–20 h

- Volume of distribution

0.13–0.15 L/kg

- Metabolism

- Main metabolic pathways

Glucuroconjugation by uridine diphosphate glucuronosyltransferases (~50%), mitochondrial β -oxydation (~40%) and P-450 oxidation (~10%)
Present but not clinically relevant
Inhibitor of cytochromes CYP2C9 and CYP3A4

- Active metabolite(s)

- Inhibitor or inducer of the cytochrome P450 system?

- Other significant pharmacokinetic interactions

Numerous interactions, in particular with other antiepileptics (e.g. phenytoin, lamotrigine, phenobarbital)

- Elimination of parent drug

Hepatic >95%, renal <3%

- Typical therapeutic range

50–100 mg/L (347–693 $\mu\text{mol/L}$)

- Potentially toxic concentration

>120 to 150 mg/L (>832–1040 $\mu\text{mol/L}$)

Pre-analytics

- Time to steady-state from beginning of treatment or change of posology
- Time for blood sampling
- Type(s) of sample
- Stability

2–4 days

Before next dose at steady state

Serum or plasma

48 h at 4°C (for longer conservation, freeze at -20°C)

Remarks

In patients with renal insufficiency the free valproic acid concentration should be determined due to reduced protein binding.

References

- Arzneimittelkompendium Schweiz, Basel: Documed 2005.
- Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, Grundlagen der Arzneimitteltherapie (16. Auflage), Basel: Documed, 2005.
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